Patent
Attorney's Docket No. 024916-011

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	
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Anthony M. JEVNIKAR et al.	)	
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Application No.: Unassigned	)	Group Art Unit: Unassigned
	)	
Filed: December 7, 2001	)	Examiner: Unassigned
	)	
For: METHODS AND PRODUCTS FOR CONTROLLING THE IMMUNE RESPONSES IN MAMMALS	)	

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination on the merits, please amend the above-identified application as follows:

IN THE SPECIFICATION:

Please insert the following paragraph after the title of the invention on page 1 of the specification:

--This application is a divisional of Application Serial No. 08/617,874, filed on May 21, 1996, which is a national stage filing under 35 U.S.C. § 371 of International Application No. PCT/CA94/00530, filed on September 21, 1994, which International Application was published by the International Bureau in English on March 30, 1995. This

application also claims benefit of foreign priority under 35 U.S.C. § 119 and/or 35 U.S.C. § 365 to Application No. 9319429.8 filed in Great Britain on September 21, 1993; the entire content of which is hereby incorporated by reference.--

In compliance with 37 C.F.R. § 1.823(a), please insert the attached paper copy of the "Sequence Listing" between the last page of the Disclosure (Page 24) and the first page of the claims (page 25).

Please insert the enclosed copy of the Abstract, which is provided on a separate sheet of paper, into the application after the last page of the claims, currently page 32.

Kindly replace the paragraph beginning at page 6, line 11, with the following:

--Figures 12A and 12B show in schematic form the construction of plasmid pSM215.

Panel A shows a map of mouse GAD65 cDNA.

Panel B shows a map of expression vector pSM215.--

Kindly replace the paragraphs beginning at page 17, line 16 through page 17, line 37, with the following:

-- The signal sequence was isolated from barley α-amylase cDNA clone as a PCR product using two synthetic primers. The forward primer (5' -CGGATCCGGCGCG

CGCCATGGGGAAG - 3') (SEQ ID NO.:1) had a BamHI site added to 5' end to facilitate cloning, and the reverse primer (5' -GGAATTCCCGGGCGCCGGACGCCAAACC CGGCGAG - 3') (SEQ ID NO.:2) contained two engineered restriction sites, EcoR1 and NarI. EcoR1 was used for convenience in subcloning whereas Nar1 provided a site for fusion. The PCR product was isolated, digested with BamHI and EcoR1, and cloned into pBluscriptII (Stratagene, an E. coli plasmid vector which does not have any NarI site), to form intermediate plasmid pBluscriptII-10.

The DNA fragment encoding the mature peptide sequence (native protein minus signal peptide) of murine II α chain was created by PCR using the following two synthetic primers: 5'- GGGCGCCGAAGACGACATTGAGGCCGAC - 3' (SEQ ID NO.:3) (forward reaction), which contained a compatible NarI site at its 5', and 5' -CGAATT CTCATAAAGGCCCTGGGTGTCT - 3' (SEQ ID NO.:4) (reverse reaction) which had an EcoR1 site attached to the 5' end. The PCR product was rescued as an EcoR1 + NarI fragment.--

Kindly replace the paragraph beginning at page 18, line 10, with the following:

--pSM156 was constructed by replacing the native signal sequence of I-A β gene with the signal sequence of barley α-amylase (Figure 2). The strategy employed was essentially the same as for the construction of pSM155. Two primers were used for the isolation of mature β gene coding sequence: 5' -GGGCGCCGAAGACGACATTG

AGGCCGAC - 3' (SEQ ID NO.:5) (forward primer) and 5'-CGAATTCTCATAAAG GCCCTGGGTGTCT - 3' (SEQ ID NO.:6) (reverse primer).--

Kindly replace the paragraph beginning at page 18, line 20, with the following:

--CONSTRUCTION OF pSM151-del: pSM151-del contains the truncated form of I-A α gene in which its DNA sequence determining the C-terminal cytoplasmic domain, was deleted, as in Figure 1. This was obtained by polymerase chain reaction-mediated amplification after a 1.1kb EcoR1 fragment was cloned into pUC19. The M13/PUC universal primer (5' - GTAAAACGACGGCCAGT-3') (SEQ ID NO.:7) is used as a forward primer. The reverse primer (5' -CGAATTCTCACAGGCCTTGAATGAT GAAGAT-3') (SEQ ID NO.:8) corresponding to I-A α encoding sequence between nucleotides 715 and 732, introduces a termination codon TGA starting at nucleotide position 733, followed by an EcoR1 cloning site. The truncated gene was amplified by 25 cycles of heating (94°C, 1min), annealing (55°C, 1.5min), and extension (72°C, 2min). The reaction product was purified, digested with EcoR1, blunt-ended with Klenow fragment, and first inserted into pSM150, and then the whole expression cassette was reisolated as a EcoR1 and HindIII fragment and subcloned into pBIN19 to give pSM151-del (Figure 2).--

Kindly replace the paragraph beginning at page 19, line 3, with the following:

--CONSTRUCTION OF pSM152-del: pSMA152-del contains the truncated I-A β gene which has its DNA sequence determining the C-terminal cytoplasmic domain removed (Figure 2). This was accomplished essentially by the same procedure as used to construct PSM151-del. The M13/pUC universal primer was used as a forward primer. The reverse primer (5' - CGAATTCTCAGATGAAAAGGCCAAGCCCGAG-3') (SEQ ID NO.:9) which is complementary to the nucleotide sequence of I-A β gene at positions 715 and 735, introduced a TGA stop codon after nucleotide 715, followed by the same EcoR1 cloning site.--

Kindly replace the paragraph beginning at page 22, line 17, with the following:

--A plasmid expression vector, pSM215, was constructed as shown in Figure 12. A NcoI restriction site as indicated in Panel A was created by site-directed mutagenesis and used as part of a translational start site. Site-directed mutagenesis was done using the reaction kit purchased from Pharmacia following manufacturer's instructions. The primer used was 5' - GACCACCGAGCCATGGCATCTTC-3' (SEQ ID NO.:10) which includes a new NcoI restriction site. The modified murine DNA was cloned into plasmid pSM150. The translation start (ATG) and stop (TGA) sites are indicated. This GAD cDNA was inserted between the cauliflower mosaic virus 35S promoter, Ehn 35S, and the transcription termination sequence of nopaline synthase (NOS-ter).--

IN THE CLAIMS

Please delete claims 1-51[1] without prejudice or disclaimer to the subject matter recited therein.

Please add new claims 52-101 as follows:

--52. A method for suppressing or reducing the immune response of a mammal to an antigen comprising:

orally or enterally administering to the mammal an effective immune suppressive dose of a plant tissue or a partially purified plant tissue extract containing said antigen or an immunosuppressive fragment thereof, said plant tissue or partially purified plant tissue extract being obtained from a transgenic plant expressing said antigen or immunosuppressive fragment thereof.

53. The method of claim 52 wherein the antigen is a mammalian autoantigen.

54. The method of claim 52, wherein the autoantigen is involved in the pathogenesis of an autoimmune disease.

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[1] The amended sheets of claims in the originally filed PCT application contained claims numbered 1-52. However, these claims were misnumbered as there was no claim numbered 44. In the parent application, the United States Patent and Trademark Office renumbered the original claims pursuant to 37 C.F.R. § 1.126 so as to be numbered 1-51. Applicants respectfully request that the Office renumber the originally filed claims in this divisional application as well so as to be numbered 1-51. Thus, the present amendment properly adds new claims beginning with claim 52.

55. The method of claim 52, wherein the autoantigen is involved in the pathogenesis of a pre-clinical stage of an autoimmune disease.

56. The method of claim 53, wherein the autoantigen is involved in the pathogenesis of a disease selected from the group consisting of lupus erythematosis, thyroiditis, multiple sclerosis, uveitis, Crohns' Disease and autoimmune diabetes, provided that the autoantigen involved in autoimmune diabetes is not glutamic acid decarboxylase.

57. The method of claim 53, wherein the autoantigen is selected from the group consisting of myelin basic protein, thyroglobulin, collagen, islet cell antigen and insulin.

58. The method of claim 53, wherein the transgenic plant is selected from the group consisting of potato, tomato, alfalfa, canola, and low alkaloid tobacco.

59. The method of claim 52, wherein the plant tissue or partially purified plant tissue extract is selected from the group consisting of at least one plant part, an extract of total plant protein, and a partially purified plant protein preparation.

60. The method of claim 52, wherein the plant tissue or partially purified plant tissue extract is from at least one plant part selected from the group consisting of leaves, stems, seeds and tubers.

61. The method of claim 52, wherein the transgenic plant is transformed with a DNA construct for transforming a plant, said construct comprising a Cauliflower Mosaic Virus Ehn-35S promoter operably linked to a DNA coding sequence and further comprising a termination sequence in proper reading frame with the DNA coding sequence, wherein the termination sequence is a nopaline synthase termination sequence and the DNA coding sequence encodes the antigen.

62. The method of claim 53, wherein the mammal is a human.

63. A pharmaceutical composition for suppressing or reducing the immune response of a mammal to an antigen comprising:

an oral or enteral dosage form comprising an effective immunosuppressive dose of a plant tissue or partially purified plant tissue extract containing said antigen or an immunosuppressive fragment thereof and a pharmaceutically acceptable carrier, said plant tissue or partially purified plant tissue extract being obtained from a transgenic plant expressing said antigen or immunosuppressive fragment thereof.

64. The composition of claim 63, wherein the antigen is a mammalian autoantigen.

65. The composition of claim 63, wherein the autoantigen is involved in the pathogenesis of an autoimmune disease.

66. The composition of claim 63, wherein the autoantigen is involved in the pathogenesis of a pre-clinical stage of an autoimmune disease.

67. The composition of claim 63, wherein the autoantigen is involved in the pathogenesis of a disease selected from the group consisting of lupus erythematosis, thyroiditis, multiple sclerosis, uveitis, Crohns' Disease and autoimmune diabetes, provided that the autoantigen involved in autoimmune diabetes is not glutamic acid decarboxylase.

68. The composition of claim 63, wherein the autoantigen is selected from the group consisting of myelin basic protein, thyroglobulin, collagen, islet cell antigen and insulin.

69. The composition of claim 63, wherein the transgenic plant is selected from the group consisting of potato, tomato, alfalfa, canola and low alkaloid tobacco.

70. The composition of claim 63, wherein the plant tissue or partially purified plant tissue extract is from at least one plant part selected from the group consisting of leaves, stems, seeds and tubers.

71. The composition of claim 63, wherein the transgenic plant is transformed with a DNA construct for transforming a plant, said construct comprising a Cauliflower Mosaic Virus Ehn-35S promoter operably linked to a DNA coding sequence and further comprising a termination sequence in proper reading frame with the DNA coding sequence, wherein the termination sequence is a nopaline synthase termination sequence and the DNA coding sequence encodes the antigen.

72. The method of claim 52, wherein the antigen is a mammalian transplantation antigen.

73. The method of claim 72, wherein the transplantation antigen is a human Major Histocompatibility Complex (MHC) protein.

74. The method of claim 73, wherein the MHC protein is selected from the group consisting of an MHC class I protein, an MHC class II protein, an MHC class IIa chain and an MHC class IIb chain.

75. The method of claim 72, wherein the transgenic plant is selected from the group consisting of potato, tomato, alfalfa, canola and low alkaloid tobacco.

76. The method of claim 72, wherein the plant tissue or partially purified plant tissue extract is from at least one plant part selected from the group consisting of leaves, stems, seeds and tubers.

77. The method of claim 72, wherein the mammal is a human.

78. The composition of claim 63, wherein the antigen is a mammalian transplantation antigen.

79. The composition of claim 78, wherein the transplantation antigen is a human Major Histocompatibility Complex (MHC) protein.

80. The composition of claim 78, wherein the MHC protein is selected from the group consisting of an MHC class I protein, an MHC class II protein, an MHC class IIa chain and an MHC class IIb chain.

81. The composition of claim 78, wherein the transgenic plant is selected from the group consisting of potato, tomato, alfalfa, canola and low alkaloid tobacco.

82. The composition of claim 78, wherein the plant tissue or partially purified plant tissue extract is from at least one plant part selected from the group consisting of leaves, stems, seeds and tubers.

83. The composition of claim 78, wherein the mammal is a human.

84. A method for suppressing the rejection of engrafted donor tissue in a recipient mammal comprising orally or enterally administering to the mammal an effective immunosuppressive dose of a plant tissue or a partially purified plant tissue extract containing a transplantation antigen of said donor tissue or an immunosuppressive fragment thereof, said plant tissue or partially purified plant tissue extract being obtained from a transgenic plant expressing said transplantation antigen or immunosuppressive fragment thereof.

85. The method of claim 84, wherein the transplantation antigen is an MHC protein.

86. The method of claim 85, wherein the MHC protein is selected from the group consisting of an MHC class I protein, an MHC class II protein, an MHC class IIa chain and an MHC class IIb chain.

87. The method of claim 84, wherein the transgenic plant is selected from the group consisting of potato, tomato, alfalfa, canola and low alkaloid tobacco.

88. A transgenic plant comprising a plant expressing a recombinant mammalian transplantation antigen.

89. The transgenic plant of claim 88, wherein the transplantation antigen is a human Major Histocompatibility Complex (MHC) protein.

90. The transgenic plant of claim 89, wherein the MHC protein is selected from the group consisting of an MHC class I protein, an MHC class II protein, an MHC class IIa chain and an MHC class IIb chain.

91. The transgenic plant of claim 88, wherein the plant is selected from the group consisting of potato, tomato, alfalfa, canola, and low alkaloid tobacco.

92. A transgenic plant comprising a plant expressing a recombinant autoantigen other than GAD.

93. The transgenic plant of claim 92, wherein the autoantigen is selected from the group consisting of myelin basic protein, thyroglobulin, collagen, islet cell antigen and insulin.

94. The transgenic plant of claim 92, wherein the plant is selected from the group consisting of potato, tomato, alfalfa, canola, and low alkaloid tobacco.

95. An edible plant material comprising a plant tissue or partially purified plant tissue extract obtained from a transgenic plant of claim 88.

96. An edible plant material comprising a plant tissue or partially purified plant tissue extract obtained from a transgenic plant of claim 92.

97. A method for preventing the development of an autoimmune disease in a mammal comprising orally or enterally administering to the mammal an effective amount of a plant tissue or a partially purified plant tissue extract containing an autoantigen associated with the disease or an immunosuppressive fragment thereof, said plant tissue or partially purified plant tissue extract being obtained from a transgenic plant expressing said autoantigen or immunosuppressive fragment thereof.

98. The method of claim 97, wherein said mammal is a human.

99. The method of claim 98, wherein said autoimmune disease is autoimmune diabetes.

100. The method of claim 99, wherein said antigen is human GAD.

101. The method of claim 97, wherein said autoimmune disease is in a preclinical stage.--

REMARKS

Entry of the foregoing and prompt and favorable consideration of the subject application, in light of the following remarks, are respectfully requested.

By the foregoing amendment, the specification has been amended to insert the information concerning the continuing and foreign priority data, to insert the paper copy of the Sequence Listing, to insert the Abstract on a separate sheet of paper and to make the disclosure consistent with regard to amendments made to the specification in the parent application. Furthermore, originally presented (and renumbered) claims 1-51 have been canceled without prejudice or disclaimer and new claims 52-101 have been added. Support for these new claims can be found throughout the originally filed application. Hence, no new matter has been added.

In the event that there are any questions relating to this Preliminary Amendment, or the application in general, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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Attachment to Preliminary Amendment dated December 7, 2001

Marked-up Copy

Page 6, Paragraph Beginning at Line 11

[Figure 12 shows] Figures 12A and 12B show in schematic form the construction of plasmid pSM215.

Panel A shows a map of mouse GAD65 cDNA.

Panel B shows a map of expression vector pSM215.

Page 17, Paragraphs Beginning at Line 16 through Page 17, line 37

The signal sequence was isolated from barley α-amylase cDNA clone as a PCR product using two synthetic primers. The forward primer (5' -CGGATCCGGCGCGC GCCATGGGGAAG - 3') (SEQ ID NO.:1) had a BamHI site added to 5' end to facilitate cloning, and the reverse primer (5' -GGAATTCCCGGGCGCCGGACGCCAAAC CCGGCGAG - 3') (SEQ ID NO.:2) contained two engineered restriction sites, EcoR1 and NarI. EcoR1 was used for convenience in subcloning whereas Nar1 provided a site for fusion. The PCR product was isolated, digested with BamHI and EcoR1, and cloned into pBluscriptII (Stratagene, an E. coli plasmid vector which does not have any NarI site), to form intermediate plasmid pBluscriptII-10.

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primers: 5'- GGGCGCCGAAGACGACATTGAGGCCGAC - 3' (SEQ ID NO.:3) (forward reaction), which contained a compatible NarI site at its 5', and 5' - CGAATT CTCATAAAGGCCCTGGGTGTCT - 3' (SEQ ID NO.:4) (reverse reaction) which had an EcoR1 site attached to the 5' end. The PCR product was rescued as an EcoR1 + NarI fragment.

Page 18, Paragraph Beginning at Line 10

pSM156 was constructed by replacing the native signal sequence of I-A β gene with the signal sequence of barley α-amylase (Figure 2). The strategy employed was essentially the same as for the construction of pSM155. Two primers were used for the isolation of mature β gene coding sequence: 5' - GGGCGCCGAAGACGACATTGAGGCCGAC - 3' (SEQ ID NO.:5) (forward primer) and 5' CGAATTCTCATAAAGGCCCTGGGTGTCT - 3' (SEQ ID NO.:6) (reverse primer).

Page 18, Paragraph Beginning at Line 20

CONSTRUCTION OF pSM151-del: pSM151-del contains the truncated form of I-A α gene in which its DNA sequence determining the C-terminal cytoplasmic domain, was deleted, as in Figure 1. This was obtained by polymerase chain reaction-mediated amplification after a 1.1kb EcoR1 fragment was cloned into pUC19. The M13/PUC universal primer (5' - GTAAAACGACGGCCAGT-3') (SEQ ID NO.:7) is used as a forward primer. The reverse primer (5' -CGAATTCTCACAGGCCTTGAA

TGATGAAGAT-3') (SEQ ID NO.:8) corresponding to I-A α encoding sequence between nucleotides 715 and 732, introduces a termination codon TGA starting at nucleotide position 733, followed by an EcoR1 cloning site. The truncated gene was amplified by 25 cycles of heating (94°C, 1min), annealing (55°C, 1.5min), and extension (72°C, 2min). The reaction product was purified, digested with EcoR1, blunt-ended with Klenow fragment, and first inserted into pSM150, and then the whole expression cassette was reisolated as a EcoR1 and HindIII fragment and subcloned into pBIN19 to give pSM151-del (Figure 2).

Page 19, Paragraph Beginning at Line 3

CONSTRUCTION OF pSM152-del: pSMA152-del contains the truncated I-A β gene which has its DNA sequence determining the C-terminal cytoplasmic domain removed (Figure 2). This was accomplished essentially by the same procedure as used to construct PSM151-del. The M13/pUC universal primer was used as a forward primer. The reverse primer (5' - CGAATTCTCAGATGAAAAGGCCAAGCCCGAG-3') (SEQ ID NO.:9) which is complementary to the nucleotide sequence of I-A β gene at positions 715 and 735, introduced a TGA stop codon after nucleotide 715, followed by the same EcoR1 cloning site.

Page 22, Paragraph Beginning at Line 17

A plasmid expression vector, pSM215, was constructed as shown in Figure 12. A NcoI restriction site as indicated in Panel A was created by site-directed mutagenesis and used as part of a translational start site. Site-directed mutagenesis was done using the reaction kit purchased from Pharmacia following manufacturer's instructions. The primer used was 5' - GACCACCGAGCCATGGCATCTTC-3' (SEQ ID NO.:10) which includes a new NcoI restriction site. The modified murine DNA was cloned into plasmid pSM150. The translation start (ATG) and stop (TGA) sites are indicated. This GAD cDNA was inserted between the cauliflower mosaic virus 35S promoter, Ehn 35S, and the transcription termination sequence of nopaline synthase (NOS-ter).